UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,396	09/26/2003	Daniel V. Santi	300622010900	9173

81228 7590 03/18/2009

Fox Rothschild LLP
Bristol-Myers Squibb
2000 Market Street
10th Floor
Philadelphia, PA 19103

EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
03/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,396	SANTI ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/31/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 69-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15 and 69-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed February 21, 2008 on December 31, 2008 is acknowledged. The Affidavit filed on December 31, 2008 has been considered.

Claim Disposition

2. Claims 1, 3-15 and 69-95 are pending and are under examination.

Maintained and Amended-Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3-15 and 69-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a synthetic gene encoding a polypeptide segment that corresponds to a reference polypeptide segment (see for example claim 1), however, the claims do not set forth said "reference polypeptide" and are devoid of a structure, especially in view of the recited sequence identity. In addition, no functional limitation is recited in the claims for the recited "polypeptide segment" described as being 90% or less or at least 95%, thus no correlation is made between function and structure. It is noted that claim 1 recites a PKS polypeptide segment; however, there is no indicia as to what said segment looks like or the reference structure. The claims also recite that the naturally occurring gene encodes a polypeptide that is 95% or 97% identical to the polypeptide segment encoded by the synthetic gene. Further, the claimed invention is directed to a coding segment of the gene that is less than 90% or 80% of the naturally occurring gene". Thus, the claims encompass a large variable genus, not adequately described. The skilled artisan cannot envision the detailed chemical structure of the genus encompassed in the claims, thus the claimed invention lacks adequate written description.

The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately

described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In addition, claims such as claim 92 provides an accession number for the organism such as erythromycin to provide a structural limitation, however, the disclosure does not provide a description of said structure, just the accession numbers.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus could include non-functional proteins or proteins with a different function than the one contemplated. Therefore, the genus of claimed polypeptides encompasses widely variant species. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional. Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that

[he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of genes and the encoded polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 1, 3-15 and 69-95 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claims 1, 85-86, 88, 90, 91, 93, 94, 95 and the dependent claims hereto are indefinite for the recitation of "synthetic gene" because it unclear how to distinguish a stretch of sequence that is synthetic from the naturally occurring one".

Claims 1, 75, 85-86, 88, 90 and the dependent claims hereto are indefinite for the recitation of "a polypeptide segment that corresponds to a reference polypeptide", as it is unclear what "reference polypeptide is being referred to because no structure is recited in the claims, especially in view of the recited percent identity. For instance, 95% identical to what structure.

Claim 7 in indefinite for the recitation of "near" because this is a relative term and it is unclear how "near" the restriction site is to the module. What is the true proximity?

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3-4, 6, 8-15, 69-71, 92 are rejected under 35 U.S.C. 102(b) as being anticipated by Khosla et al. (U.S. Patent No. 6, 066,721, December 21, 1999), based on the breath of the claims.

The claimed invention is directed to:

"A synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene, and

a) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are the same length and comprise at least 50 amino acids;

b) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence; and

c) the polypeptide segment encoding sequence of the synthetic gene and the polypeptide segment encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence,

d) the polypeptide segment encoded in the synthetic gene retains the activity of the

polypeptide segment encoded by the naturally occurring gene;
and at least one of:
e) the polypeptide segment-encoding sequence of the synthetic gene is free from at least one Type IIS enzyme restriction site present in the polypeptide segment-encoding sequence of said naturally occurring gene; or

f) the polypeptide segment-encoding sequence of the synthetic gene is different from the polypeptide segment-encoding sequence of said naturally occurring PKS gene and comprises at least two of:

i) a Spe I site near the sequence encoding the amino-terminus of the module;

ii) a Mfe I site near the sequence encoding the amino-terminus of a KS domain;

iii) a Kpn I site near the sequence encoding the carboxy-terminus of a KS domain;
iv) a Msc I site near the sequence encoding the amino-terminus of an AT domain;
v) a Pst I site near the sequence encoding the carboxy-terminus of an AT domain:
vi) a BsrB I site near the sequence encoding the amino-terminus of an ER domain;
vii) an Age I site near the sequence encoding the amino-terminus of a KR domain:
viii) an Xba I site near the sequence encoding the amino-terminus of an ACP domain.

The instant claim 1 as set forth above can be read very broadly since "gene" comprises structures with or without a promoter and the claim reads on any gene cluster having a catalytic domain. In addition, the claim as amended recites "at least one of "(emphasis added) and lists items (e) and (f), thus finding the limitation of (e) is all that is required.

Khosla et al. teach methods to prepare a polyketide synthase gene cluster in which the ketosynthase domain in module 1 (KS1) is inactivated (see claim 1 and paragraph 11 of the patent), thus producing a mutated or modified gene cluster. In addition, Khosla et al. teach a recombinant plasmid vector which comprises an

expression system for production of polyketide synthase (PKS) wherein said expression system comprises a nucleotide sequence encoding a functional modified modular PKS operatively linked to control sequences for expression of said modified PKS containing at least a first and second module, (wherein said modification inactivates the ketosynthase (KS) catalytic domain of the first module), thus anticipates claims 1, 3-4, 8-9 and 11-15 (see for example claims 3-7 of the patent). Instant claim 6 is also anticipated since Khosla et al. is silent on Type IIS enzyme restriction, thus would meet the claim limitation of being "free" of said restriction enzyme (see also claim 1 (e) of the instant application). Further, Khosla et al. teach that said inactivation is by modification of a single codon of said catalytic domain, wherein said codon, in its unmodified form, encodes cysteine, and wherein said codon in its modified form encodes alanine (see for example claims 3-7 of the patent), thus a preferred codon is selected. Moreover, Khosla et al. teach a vector wherein said modules are modules of the *erythromycin* PKS gene cluster (see instant claim 92). The patent also discloses that the control sequences are heterologous to the encoding nucleotide sequence. Therefore, the limitations of the claims are met by the reference.

6. Claims 1, 3-4, 6, 8-15, 69-71 and 92 are rejected under 35 U.S.C. 102(b) as being anticipated by Katz et al. (U.S. Patent No. 6,004,787, December 21, 1999), based on the breath of the phrase "synthetic gene" recited in the claims.

The claimed invention is directed to:

"A synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene, and

a) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are the same length and comprise at least 50 amino acids;

b) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence; and

c) the polypeptide segment encoding sequence of the synthetic gene and the polypeptide segment encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence",

d) the polypeptide segment encoded in the synthetic gene retains the activity of the

polypeptide segment encoded by the naturally occurring gene;
and at least one of:
e) the polypeptide segment-encoding sequence of the synthetic gene is free from at least one Type IIS enzyme restriction site present in the polypeptide segment-encoding sequence of said naturally occurring gene; or

f) the polypeptide segment-encoding sequence of the synthetic gene is different from the polypeptide segment-encoding sequence of said naturally occurring PKS gene and comprises at least two of:

i) a Spe I site near the sequence encoding the amino-terminus of the module;

ii) a Mfe I site near the sequence encoding the amino-terminus of a KS domain;

iii) a Kpn I site near the sequence encoding the carboxy-terminus of a KS domain;
iv) a Msc I site near the sequence encoding the amino-terminus of an AT domain;
v) a Pst I site near the sequence encoding the carboxy-terminus of an AT domain:
vi) a BsrB I site near the sequence encoding the amino-terminus of an ER domain;
vii) an Age I site near the sequence encoding the amino-terminus of a KR domain:
viii) an Xba I site near the sequence encoding the amino-terminus of an ACP domain.

The term gene can be broadly interpreted as having a promoter or not and the term "synthetic" can demonstrate the hand of man using PCR or codon opitimization or genetic engineering. The claim can thus be broadly read as "a polynucleotide encoding a polypeptide segment...". In addition, the claim as amended recites "at least one of "(emphasis added) and lists items (e) and (f), thus finding the limitation of (e) is all that is required.

Katz et al. teach a method to produce novel polyketide structures by designing and introducing specified changes in the DNA governing the synthesis of the polyketide accomplished by introducing one or more specified changes into the DNA sequence, thus a synthetic gene. The method of Katz et al. is disclosed as most useful when the segment of the chromosome modified is involved in polyketide biosynthesis, particularly for manipulation of polyketide synthase genes (derived from *erythromycin*), see columns 2-3 of the patent. Katz et al. also teach PKS domains such as AT and ACP, and teach PKS modules (see column 3 of the patent). Katz et al. is silent on "TypeIIS", thus would inherently be "free of TypeIIS". The method of Katz et al. utilizes restriction enzymes such as SphI and PstI (paragraph [0064] of the patent). Katz et al. discloses a gene cluster 6-deoxyerythronolide from *S. erythraea* (see paragraph 172 of the patent), which has a native thioesterase II. Claims directed to vectors and host cells are anticipated since expression vectors and cells are used in the patent (see paragraph [0017]). Further claims reciting a synthetic gene with a certain percent identity to the encoding gene are anticipated since following manipulation of the DNA structure the gene of Katz et al. would not be 100% identical to the native structure. Therefore, the limitations of the claims are met by the reference.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

8. Claims 1, 3-15, 69-71, 74-75, 77-82, 85-95 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Katz et al. (U.S. Patent No. 6,004,787, December 21, 1999) in view of Kim et al. (Gene, vol. 199, pages 293-301, 1997).

Katz et al. teach a method to produce novel polyketide structures by designing and introducing specified changes in the DNA governing the synthesis of the polyketide accomplished by introducing one or more specified changes into the DNA sequence. The method of Katz et al. is disclosed as most useful when the segment of the chromosome modified is involved in polyketide biosynthesis, particularly for manipulation of polyketide synthase genes (derived from *erythromycin*), see columns 2-3 of the patent. Katz et al. also teach PKS domains such as AT and ACP, and teach PKS modules (see column 3 of the patent). The method of Katz et al. utilizes restriction enzymes such as SphI and PstI (paragraph [0064] of the patent). Katz et al. discloses a gene cluster 6-deoxyerythronolide from *S. erythraea* (see paragraph 172 of the patent), which has a native thioesterase II. Katz et al. renders obvious claims directed to vectors and host cells since expression vectors and cells are used in the patent (see paragraph [0017]). Katz et al. also render obvious claims reciting a synthetic gene with a certain percent identity to the encoding gene since following manipulation of the DNA structure the gene of Katz et al. would not be 100% identical to the native structure. Claims reciting a length of at least 100 amino acid residues is also obvious since the phrase "at least" has no upper boundary and the structure of the encoding genes are well established in the art. The recitation of a gene that comprises 500 to 50,000 base pairs is obvious since the gene of Katz et al. falls within that range (see the sequence listing in the patent).

Katz et al. disclose variations and modifications of the methods for obtaining the desired plasmids, hosts for cloning and choices of vectors and segments of *eryA* DNA

to clone and modify, that result in substantially the same strains and same products as those described herein. For example, the use of the plasmids pWH3 and pWHM4 as *E. coli-Sac. erythraea* shuttle vectors. In addition, Katz et al. discloses other vectors can be employed wherein all or part of pWHM3 or pWHM4 is replaced by other DNA segments that function in a similar manner, such as replacing the pUC19 component of pWHM3 and pWHM4 with pBR322, available from BRL, employing different segments of the pIJ101 or pJV1 replicons in pWHM3 and pWHM4, respectively, or employing selectable markers other than thiostrepton- and ampicillin-resistance. This disclosure renders claim 10 as obvious since the art recognizes that a library includes a population of vectors having different/heterologous nucleic acids. Claims such as claim 88 are obvious especially in view of the product by process nature of the claim, since Katz et al. teach the claimed synthetic gene and the recited length has no upper limit. Further, the manipulation of the gene by Katz et al. renders the gene as "synthetic". In addition, claim 76 is also obvious since the aforementioned disclosure in the Katz et al. patent could achieve the recited limitations (see paragraph 176 of Katz et al.). The Katz et al. patent does not explicitly teach codon optimization, however, Kim *et al.* teach that selective codons in a given gene positively correlate with its expression efficiency, (see 293 of the reference). In addition Kim et al. teach the codon optimization of a leader sequence leads to further enhancement of synthetic genes, (see page 297, right column, section 3.3).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a synthetic gene encoding a polypeptide

and methods of producing same, that corresponds to a reference polypeptide, wherein said polypeptide is encoded by a naturally occurring PKS gene as recited in claim 1 for example because Katz et al. teach the manipulation of PKS gene structures and Kim et al. teach codon optimization for enhancement of synthetic genes. Furthermore, the instant specification discloses at paragraph [0024] that "[I]n a method for designing a synthetic gene in accordance with the present invention a reference amino acid sequence is provided and reverse translated to a randomized nucleotide sequence which encodes the amino acid sequence using a random selection of codons which, optionally, have been optimized for a codon preference of a host organism. One or more parameters for positions of restriction sites on a sequence of the synthetic gene are provided and occurrences of one or more selected restriction sites from the randomized nucleotide sequence are removed. One or more selected restriction sites are inserted at selected positions in the randomized nucleotide sequence to generate a sequence of the synthetic gene.

[0039] Identifying positions of preselected restriction sites in the randomized nucleotide sequence, identifying an ability of one or more codons comprising the nucleotide sequence of the restriction site for accepting a substitution in the nucleotide sequence of the restriction site wherein such substitution will (a) remove the restriction site and (b) create a codon encoding an amino acid identical to the codon whose sequence has been changed, and changing the sequence of the restriction site at the identified codon.... [0138] Methods for reverse translation are well known".

Thus, one of ordinary skill in the art would be motivated to produce a synthetic

gene with a reasonably expectation of success based on the teachings of Katz et al. because the reference demonstrates the manipulation of gene structures encoding known proteins and Kim et al. as well as the instant specification acknowledges the usage of codon optimization to enhance the expression of a protein of interest. Moreover, the Kim et al. reference is relied upon for the teaching that the expression of a native human gene can be highly optimized by replacing the non- and un-preferred codons with preferred codons. Kim et al. teaches that despite the increased content of CpG dinuclutide in the synthetic gene relative to the wild type human gene, the synthetic gene is expressed at high levels in human cells (see Figure 2 on page 295 of the Kim et al. reference which discloses optimized sequences of the human coding sequence of the mature human erythropoientin (EPO)). The vast majority of the codon changes resulted in the substitution with G or C leading to increase the content of the CpG pair. Kim et al. teach the expression of the synthetic gene optimized with human preferred codons expressed at higher levels than that optimized with yeast codons (see the paragraph bridging the two columns on page 297). One of ordinary skill in the art would be motivated to combine the teaching of Katz et al. and Kim et al. because Kim et al. teach that since the gene optimized with human codons in human cell expresses at a higher level than that optimized with yeast codons, the ordinary skill in the art would have come to the conclusion that optimizing the signal peptide coding sequence with human codons would enhance the expression even further. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Response to Applicant's Arguments:

9. Applicant's arguments have been fully considered, however are not persuasive. Note that the rejections of record remain for the reasons stated above and herein. On page 21 of the response applicant state that " MPEP 2164.05 states that applicant need not disclose what is well known in the art. Applicant further state that even if some research and/or mental steps are required to determine what has been invented, this fact does not mean that the claim is non-compliant with the written description requirement." Applicants also state that "...it is within ordinary skill of the art to access the amino acid and nucleotide sequences of naturally occurring PKS genes, which are available in multiple databases and to identify the naturally occurring PKS genes and segments thereof, which are the closet to the segments at issue" (see page 23 of the response).

This argument is not persuasive because claim 1 for example is directed to a polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoded by the naturally occurring gene are less than 90% identical in nucleotide sequence" (see claim 1 (c)); and the language of this limitation encompasses structures such as 85%, 75%, 65%, 55%, 45%, 35%, 25%, 15%, 5%, 1%, 0% etc. Thus there is no structure-function correlation made in the claims or specification for the large variable genus claimed. The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description

of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In addition, the MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious,"

and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966."Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents" of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the

genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for *a prima facie* case is discussed below.

Further, to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: a) the scope of the invention; b) actual reduction to practice; c) disclosure of drawings or structural chemical formulas; d) relevant identifying characteristics including complete structure, partial structure, physical and/or

chemical properties, and structure/function correlation; e) method of making the claimed compounds; f) level of skill and knowledge in the art; and g) predictability in the art.

Applicant also state that the specification teaches that the naturally occurring genes are known (see page 25 of the response). However, the claims are directed to a 'synthetic' gene encoding a 'polypeptide segment' wherein said polypeptide segment corresponds to a reference polypeptide segment. How much does it correspond? A skilled artisan cannot determine what that polypeptide segment looks like.

Applicant also asks the examiner to point out where in the MPEP there is a requirement to disclose all species of a claimed genus. Applicant is reminded that the written description requirement above indicates that a representative number of species must be disclosed. Based on the large variable genus encompassed in the claims, applicants have not fulfilled that requirement and therefore do not demonstrate possession of the genus. Thus the rejection remains.

The rejection under 35 USC 112, second paragraph remains. Applicant state that "...the gene segment should only differ by 10%". This argument is not persuasive, note that item (c) of claim 1 recites 'less than 90% identical' which is contrary to applicant's statements, since the synthetic and the naturally structures could essentially only be 1% or 0% identical.

The rejection pertaining to percent language with no corresponding sequence is traversed. Applicants state that Accession numbers are provided for ORFs of different PKS genes. The issue here is that independent claim 1 for example has to stand on its

own and does not presently have a structural limitation with the recited percent language.

Applicant state that the word "near " has a clear meaning. This is not persuasive as the limitations of the specification cannot be read into the claims and this is a relative term. Therefore, the rejection remains.

Note that the art rejections remain. Applicant argues that not all limitations are taught and then indicate that in the interest of expediting the prosecution of the instant application, claim 1 has been amended to include, in the alternative, the limitations of claims 6 and 7. This amendment was insufficient to obviate the art rejections of record as the limitations as stated by applicant are in the alternative. As they are not required to be in the claimed invention, therefore, the references still apply.

Conclusion

10. No claims are allowable.

11. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed, can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652